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1 **Efficacy and safety of artificial urinary sphincter (AUS): results of a large multi-**
 2 **institutional cohort of patients with mid-term follow-up.**

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1 **ABSTRACT**

2 **AIMS:** To assess efficacy and safety as well as predictive factors of dry rate and freedom from surgical
3 revision in patients underwent AUS placement. The artificial urinary sphincter (AUS) is still
4 considered the standard for the treatment of moderate to severe post-prostatectomy stress urinary
5 incontinence (SUI). However, data reporting efficacy and safety from large series are lacking.

6 **METHODS:** A multicenter, retrospective study was conducted in 16 centers in Europe and USA. Only
7 primary cases of AUS implantation in non-neurogenic SUI after prostate surgery, with a follow-up of at
8 least one year were included. Efficacy data (continence rate, based on pad usage) and safety data
9 (revision rate in case of infection and erosion, as well as atrophy or mechanical failure) were collected.
10 Multivariable analyses were performed in order to investigate possible predictors of the aforementioned
11 outcomes.

12 **RESULTS:** Eight hundred ninety-two men had primary AUS implantation. At 32 months mean
13 follow-up overall dry rate and surgical revision were 58% and 30.7%, respectively. Logistic regression
14 analysis showed that patients without previous incontinence surgery had a higher probability to be dry
15 after AUS implantation (OR: 0.51, p=0.03). Moreover institutional case-load was positively associated
16 with dry rate (OR: 1.18; p=0.005) and freedom from revision (OR: 1.51; p=0.00).

17 **CONCLUSIONS:** The results of this study showed that AUS is an effective option for the treatment of
18 SUI after prostate surgery. Moreover previous incontinence surgery and low institutional case-load are
19 negatively associated to efficacy and safety outcomes.

21 INTRODUCTION

22 The most common radical treatment for localized prostate cancer is radical prostatectomy (RP);
23 however, major morbidities of this procedure includes stress urinary incontinence (SUI). Rates of
24 postoperative SUI has been reported to range from 6% to 52%, most typically estimated as 6.3% -
25 19.3% [1]. Risk of SUI after transurethral treatment of benign prostatic obstruction has been estimated
26 to be approximately 1% [2]

27 The European Association of Urology (EAU) Guidelines for Urinary Incontinence still considers AUS
28 implantation the standard treatment for moderate-to-severe SUI in men [3]. This recommendation,
29 however, is based on systematic reviews without high quality evidence (level 2b – 3), except for one
30 small randomized clinical trial comparing AUS with bulking agents [4–6].

31 The most commonly used device is the AMS 800™ (Boston Scientific, Marlborough, MA, USA).
32 Based on retrospective and prospective single institution cohort studies, the AUS procedure has a high
33 satisfaction rate (>80% over 4 years), which, however, is tempered by high revision rates (14-44% over
34 2 years) [7–20]. Indeed, only two prospective studies, accounting for 125 patients with a follow up of >
35 12 months, have been published [21–25]. Therefore, risk factors for efficacy or revisions rates remain
36 uncertain. Moreover, only 17% of primary implants are performed by high volume centers (performing
37 more than 10 implants per year) [22,26,27].

38 The aim of this study was to analyze the efficacy and safety of AUS in a large multi-institutional cohort
39 of patients with medium term follow-up. We also performed a multivariable analysis to assess
40 predictive factors of dry rate and freedom from surgical revision.

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3 42 **MATERIAL AND METHODS**
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6 43 Following an initiative from the Young Academic Urologists Working Party (YAUWP) of the EAU, a
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8 44 retrospective study was initiated. A common database of all cases of AUS implantations in men for
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10 45 non-neurogenic SUI following prostate surgery between 1989 and 2012 was established. A common
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12 46 template for data collection was created by the Functional Urology Group of the YAUWP and was sent
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14 47 out to all participating centres. No exclusion criteria regarding healthcare centres were applied. Only
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16 48 primary cases of AUS implantation in men for non-neurogenic SUI after prostate surgery, implanted
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18 49 via a perineal approach, with a follow-up of at least one year and with complete data on pad count and
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20 50 complications were included in the data collection phase. Pre-operative patient demographics and
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22 51 comorbidities as well as peri-operative data were collected. Post-operative data included events related
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24 52 to activation (success, delay or failure), early complication (reoperations and readmissions before
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26 53 activation), and follow-up data until last visit, including length of follow-up, SUI status (dry status,
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28 54 number of pads per day), number of revisions, complications (date and type). Data were collected by a
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30 55 single medical staff member per center, returning them anonymously to a single author that collected
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32 56 all data in a unique dataset, which was not further widespread. Data from the statistical analysis were
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34 57 shared between authors. FIG 1. At the end of data collection process, 931 cases were collected from 16
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36 58 different institutions, and after review, 892 AUS patients, with at least 1 year follow up, were included
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38 59 in the final analysis (mean 56 per institution, median 38.5, range 15-266). Data on urodynamic
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40 60 examination were available for 450/892 (50,4%) of patients.
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43 61 The main outcomes of the study were continence rate (based on pad usage) and complications
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45 62 (revisions and explantations). Social continence, defined as one pad or less/day, represents the most
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47 63 commonly used outcome in the AUS surgery literature. However, it has been criticized as even the use
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49 64 of one pad diminishes the quality of life perceived by the patient, and thus complete dryness may be the
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most patient relevant outcome [28]. Therefore in our study, we defined efficacy as dry rate (DR): namely 0 pad/day. The rate of surgical revision (SR) was defined as the need for surgery due to recurrent incontinence or complications [25].

The following variables were studied as potential predictors for efficacy (dry rate) or freedom from surgical revision: age, presence of diabetes mellitus (DM), use of anticoagulation therapy, previous incontinence surgery (PIS), previous pelvic radiotherapy (RT), use of a double cuff, cuff size, institutional case load (ICL – total number of cases per center in the whole time lapse). Moreover a further sub-analysis on the association between the average number of cases per center per year and dry rate and freedom from surgical revision was performed.

We also evaluated the global complication rate (CR), including all cases of infection and erosion, as well as failure rate (FR), including all cases of urethral atrophy (typically presumed when SUI recurrence occurs during follow up with a functioning AUS) or mechanical failure (in any of the sphincter components, tubing or one of the connections). We evaluated the proportion of patients undergoing surgical revision for the aforementioned reasons.

Chi-square and Wilcoxon rank test were used to compare the TURP and RP groups. Kaplan–Meier analysis was used to estimate incontinence rates over time. The institution caseload for dry rate and surgical revision was modeled as natural log function and constant. Institutional case load was dichotomized according to the most informative cut-off predicting dry rate and revision rate. A caseload plateau was defined as an improvement in the outcomes <1% in the subsequent 50 procedures. Multivariable logistic regression analysis was used to identify the predictors of dry rate and freedom from surgical revision rate, and to assess the role of case-load on efficacy and safety outcomes. All analyses were performed using SPSS, IBM, Armonk, USA.

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87 **RESULTS**

88 Descriptive characteristics of the cohorts are presented in Table 1. The majority of patients (85.9%)
89 previously underwent RP and others (14.1%) underwent surgery for benign prostatic obstruction. Both
90 groups were homogeneous in terms of age, previous incontinence surgery, RT, double cuff and cuff
91 size. Mean follow up after primary AUS implantation was 32 months (median 20, range 12-300).
92 Median patient age was 68 years (range 39-87). A significant statistical difference was observed in the
93 use of anticoagulants and presence of DM (Table 1). Data on history of DM and anticoagulation
94 therapy were available for all 892 patients. A history of DM was observed in 111/892 (12.4%) patients.
95 At the moment of AUS implantation, 217/892 patients (24.4%) were taking anticoagulants or
96 antiplatelet therapy. Data on preoperative antibiotics usage were available for 621/892 (69%), among
97 them, preoperative prophylaxis was used in 181 patients (29%). Among the 168 patients (19%) who
98 had undergone PIS, 75 had male sling implantation and 93 had peri-urethral balloons. Overall 257/892
99 (28.9%) patients also had adjuvant RT after prostatic surgery and prior to AUS implant; Among
100 patients treated with TURP 30% had also RT. This can be explained by the fact that some patients
101 treated with TURP were submitted to RT in case of prostate cancer incidental finding. Moreover some
102 patients treated with RT for prostate cancer could have been treated subsequently with TURP for
103 obstructive symptoms. A 4.5cm single cuff was implanted in 46.5% of patients, while 9.4% of patients
104 were implanted with double cuff in 4 different centres.

105 Data on pre-operative number of pads were available for 547/892 patients (61.3%). At the time of
106 surgery a total of 369/547 (67.2%) patients were using ≥ 5 pads/day (median 5, IQR 5-7), 20/547
107 (3.6%) used only 1 pad, 29/548 (5.3%) used 2 pads; 49/547 (8.9%) used 3 pads and 81 (14.8%) used 4
108 pads. Data on postoperative pad count were available for all patients.

Complications were reported in 248 (27.8%) patients: 60 patients (6.7%) had erosion, 38 (4.2%) infection, 32 (3.5%) were diagnosed with urethral atrophy and 118 (13.2%) with mechanical failure.

Overall dry rate and surgical revision were 58% and 30.6%, respectively. Figure 2 depicts the rate of incontinence over time. Of the 248 patients experiencing complications/failure, all but one (with mechanical failure) underwent surgical revision. The reason for revision was not available in 26/273 patients (9.5%).

Of 724 patients without PIS, 409 (57%) were dry, while of 168 with PIS, 80 (48%) achieved this goal after surgery and 88 (52%) did not. Among the 88 PIS wet patients, 27 had undergone male sling implant (30.6%) and 61 periurethral balloons (69.4%).

The best cut-off for dry rate and surgical revision was 39 and 42 respectively. Patients treated in centers with a ICL ≥ 39 resulted to achieve a significantly higher dry rate while patients treated in centers with a ICL ≥ 42 resulted to have significantly lower rates of surgical revision. Adjusted differences in dry rate and surgical revision according to institutional caseload are depicted in FIGURE (3 -4).

Multivariable logistic regression accounting for the aforementioned variables, namely: previous incontinence surgery, RT, double cuff implantation, cuff size, DM, anticoagulation therapy and ICL, showed that patients without PIS had a higher probability to be dry after AMS 800 implantation (OR: 0.51, $p=0.03$). Moreover ICL was positively associated with dry rate: higher volumes give higher continence rates (OR: 1.18; $p=0.005$). Other variables did not have statistically significant correlation with success (table 2). Institutional case load was the only variable statistically associated with freedom from surgical revision (OR: 1.51; $p=0.00$) (table 2).

In an additional analysis taking into account the average number of cases per institution per year, we showed that it positively correlates with dry rate (OR 1.05; $p=0.005$) and with freedom from surgical

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3 131 revision (OR1.075, p=0.00), confirming the evidence that higher volumes give higher continence rates
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DISCUSSION

This is the first study to report mid-term outcomes following primary AUS implantation in a large, multinational cohort of patients with non-neurogenic SUI treated in both low and high volume centres with the last modification of the system (narrow back cuff). Most earlier publications have been single centre cohort studies from high volume centres including both primary AUS implants as well as revision cases [19]. At the moment we have data about baseline safety and efficacy of primary AUS implantation, but most of them come from smaller series. Furthermore, risk factors for AUS failure or complications are not well defined.

In our multinational study, after a minimum follow-up of 12 months, overall dry rate was 58%. The global revision rate was 31%. These results are in line with studies previously reported in the literature [19]. However, many different criteria have been used, without clear consensus about the definition of efficacy and safety after surgery. External comparison of outcomes with previously published studies is therefore difficult.

In our population, 29% of patients had undergone pelvic RT. Among them, 53% were considered dry, while 30% required surgical revision after AUS placement. The influence of RT on AUS implantation outcomes remains controversial. In a meta-analysis of 15 studies including 1886 patients, men with history of pelvic RT were at higher risk of surgical revision (risk ratio of 1.56, 95%CI 1.02–2.41 $p < 0.05$, $I^2 = 82.0\%$). The need for surgical revision was higher in the RP+RT population than in the RP patients (37.3%, 95%CI 23.4–51.1 vs. 19.8%, 95%CI 11.9–27.6; $p < 0.01$). Persistence of UI after AUS placement was higher in the RP+RT population than in the RP patients 29.5%, 95% CI 18.1–45.8 vs. 12.1% 95% CI 5.7–18.4 ($p = 0.003$) [29]. In a retrospective analysis of AUS implants complicated by cuff erosion, Kaufman et al. evidenced a negative relationship between history of RT and device survival (mean device survival in RT patients 1.00 years 95% CI 0.36–3.00 vs 3.15 years 95% CI 1.95–

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3 157 5.80) [30]. These findings are in contrast with our results. Differences in radiation doses, field
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5 158 delineation, radiation technology, could account for some of the observed variability. A recent
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7 159 retrospective study on 1632 men implanted with AUS, of whom 274 had a history of RT, evidenced
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10 160 that RT does not influence re-implantation-free and revision/removal-free survival (log rank test
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12 161 $p=0.37$ vs 0.052) [31], confirming our results.
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15 162 Our analysis shows that PIS has a negative impact on dry rate ($p=0.03$), but not on freedom from
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18 163 surgical revision ($p=0.30$). In particular patient with previous incontinence surgery have a dry rate rate
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20 164 that is roughly 10% lower compared to the counterpart (48% vs. 57%). Therefore, when planning less
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22 165 invasive surgery (i.e. slings or balloons) the patient should be informed about the possible lower
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25 166 efficacy after a secondary AUS placement. On the other hand, the revision rates in this group are
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27 167 reassuring. Even in case of previous surgery, the risk of surgical revision, due to complication or
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29 168 failure, does not increase. In a small prospective case series assessing clinical results of AUS
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32 169 placement after failure of male sling surgery, mid-term results evidenced that results of this procedure
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34 170 are comparable to first-line AUS implantation in terms of continence (87%) and complications (17%)
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36 171 [32]. In a case series of 61 men after a failed primary male sling procedure, continence was higher with
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39 172 placement of an AUS, rather than by a secondary sling procedure (treatment failure of 6% and 55%
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41 173 respectively) [33].
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44 174 We demonstrated that institutional caseload is associated to dry rate and surgical revision. A median
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46 175 ICL above 39 and 42 is a protective factor in terms of dry rate and surgical revision respectively.
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49 176 Moreover, we demonstrated that 150 cases are required to reach a plateau for both outcomes. Even
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51 177 though it is true that “practice makes perfect,” only an improvement $<1\%$ was observed in the
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53 178 subsequent 50 cases. According to these data, patients treated in high volume centers are more likely to
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be dry and free from revisions and, in experienced hands (surgeons above 150 procedures), the outcome does not change appreciably.

In a single-center, single-surgeon, continuous series of implants, Lai et al. demonstrated that the number of complications and reoperations decreases after having performed the first 25 procedures in his experience (12 complications in the first 25 procedures vs. 3 in the following 25, relative risk 4.0, $p=0.012$; 11 vs. 3 reoperations, relative risk 3.7, $p=0.026$)[34]. Another study showed that the learning curve for AUS placement has no plateau, with reduction of revisions even after 200 procedures: the risk of revision within 5 years from implant was estimated at 24% after the first 5 procedures, 18% after 100 procedures and 13% after 200 procedures. The same study also showed that the majority of patients are treated in smaller volume centres: two-thirds of patients were operated by surgeons with an experience of less than 25 AUS implants, and only 9% of patients were operated by highly experienced surgeons having performed more than 100 AUS implants [35].

Our results suggest that neither the presence of a double cuff nor cuff size influence the two main outcomes: dry rate and freedom from surgical revision. The choice of the cuff size is mainly made at the surgical table and there are no standardized criteria, thus it has been advocated as a surgeon-dependent risk factor for post-operative incontinence and complications. We feel to underline that the surgical technique of AUS implant is amenable of different procedural variations that influence the standardization of the technique. We partially reduced this heterogeneity with the inclusion of perineal surgical access only, but there still remains variability in terms of site of cuff implant (bladder neck or bulbar urethra), number of cuffs implanted (single or double) and cuff size.

In a prospective multicentre cohort including 386 patients, the positioning of a 3.5 cm cuff was related to a higher risk of device explantation. [36]. However, in a retrospective cohort of 1082 patients, a cuff

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3 201 greater than 5.0 cm was also associated with a higher revision rate compared to smaller sizes (HR 2.91,
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5 202 95%CI 1.92-4.25, $p < 0.001$) due to an increased number of complications [37].
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9 203 In partial agreement with our results, in a study of 56 patients the use of a double cuff implant did not
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11 204 result in improved long term continence nor in quality of life. Furthermore, the rate of complications
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13 205 was doubled in the population implanted with double cuff (7 vs. 12 events). In another group of 180
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15 206 patients it was demonstrated that no significant objective improvement on postoperative daily pad use
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18 207 (continence 71% single cuff, 83% double cuff, $p=0.05$), however patients seemed to be better satisfied
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20 208 with a double cuff implant (superior subjective cure rate: 78% single cuff vs. 91% double cuff, $p=0.02$;
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22 209 superior social continence: 84% single cuff vs. 98% double cuff, $p=0.001$) even if at the expected of a
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24 210 higher risk of device explantation [24,38].
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28 211 With our findings, we demonstrated that a higher institutional caseload reduces the impact of operator-
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30 212 dependent factors on outcome.
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33 213 Data on antibiotic therapy were available only for 621 patients. Antibiotic use lacks of a standard
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35 214 procedure for all centers, as its choice is influenced by local resistance trends and local protocols.
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38 215 Perioperative antibiotic prophylaxis has been demonstrated to be effective in reducing infections rates,
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40 216 based on studies on orthopedic prosthetic surgery [39]. However, recently, Adamsky et al. evidenced in
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42 217 a large cohort of 3594 AUS implants that nearly one third of patients (61.1%) are prescribed
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45 218 postoperative antibiotic therapy and that it does not reduce the odds of AUS explant [40].
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48 219 Diabetes mellitus is a reported risk factor for prosthesis infection [41]. Anticoagulant therapy is a
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50 220 known risk factor for bleeding complications, which in turn, can lead to infection and erosion. Very
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52 221 few data are available on the correlation of anticoagulation therapy and AUS outcomes. A recent study
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55 222 conducted on 506 patients demonstrated that DM was associated with a higher incidence of impaired
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57 223 wound healing after AUS implant (7.3 vs. 1.7%, $p=0.003$), but no correlation to dry rate and revision
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rate was reported [42]. Another cohort of AUS patients (n=954) showed that among diabetic patients, the incidence of infection and erosions at 5 years was higher compared to those without diabetes (13% vs. 8%; $p=0.025$); however, there was no difference between diabetic patients and controls in terms of social continence (45% vs. 57%; $P=0.29$) and subjective satisfaction (95% vs. 90%; $p=0.43$) [41].

Our overall and specific complication rate is in line with a recently published review on AUS safety: infection rate ranged from 0.5 to 10.6%, erosion rate ranged from 2.9% to 12%, urethral atrophy rates ranged from 1.6% to 11.4%, mechanical failure rates ranged between 5% and 29% [17], [37]. Lai et al. demonstrated that infection and erosion tend to be early events with a mean time to event of 3.7 and 19.8 months respectively; atrophy and mechanical failure tend to be late events with a mean time to event of 29.6 and 68.1 months respectively. Although the risks of infection and erosion reached a plateau over time, the risks of urethral atrophy and mechanical failure increased over time, as they are related to the compressive effect of the device and deterioration of mechanical components [12,34].

Several aspects of our data are noteworthy. This is the largest retrospectively collected cohort of men undergoing primary AUS with medium-term follow-up reported in the literature. By including only “virgin” AUS implants, our study eliminates possible confounding factors from re-interventions. All patients were counseled in a tertiary referral center for the surgical treatment of incontinence, and we were able to prove that even among tertiary referral centers there is a significant variability in terms of outcomes according to the number of implants performed per year. This underlines the need for accurate counseling of the patient.

The study also has some limitations. First, data were collected retrospectively from patients and surgeons’ reports and some collection bias cannot be excluded. We included in the database only patients with complete data on continence and complications at last follow-up, with a possible selection bias; the success rates only accounts for patients with the device in place at least 1 year. No

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248 standardized method was used to assess the severity of incontinence pre-operatively or the urinary
249 outcomes after surgery. We had no information on the follow-up regimen for each center; the analysis
250 was made on data available at last follow up.

CONCLUSION

This multicenter study has shown continence outcomes in line with previous studies, defining AUS as an effective treatment for moderate to severe male (post-prostatectomy) SUI with complete continence in 58% of patients. We report PIS as a risk factor for decreased efficacy of surgery. Revision rate (30.7% after mid-term follow-up) was impacted by Institutional caseload but not by other patient characteristics. These results should be confirmed by an international prospective study. The SATURN registry [43] should hopefully rectify this.

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Reviewer: 1

1. The only information needed for a time-event model, such as a Kaplan Meier analysis, is the time to last follow-up and whether the patient is censored or was a failure at that time point. Thus, performing the analysis should be feasible, even in the current dataset. This would be a useful addition to the paper.

Thank you for your comment. Since we have data on time to last follow-up we could perform the analysis on the dry rate over time as you suggested. This was not possible for revision rate since we don't have data on time to revision. We included figure number 2 with the Kaplan Meier analysis.

2. Excluding patients that failed before 12 months, for instance those that had an infection in the first few months, will artificially inflate the success rates. Would add this as a limitation, that the success rates only account for patients with the device in place at least 1 year.

Thank you for your comment. We included this limitation in line 254.

3. Would remove the comment that the study included "single surgical teams" for each institution, since it is overly vague. The authors report that they can't specify the number of surgeons that performed the cases at each institution. It is likely there were multiple surgeons and thus, multiple surgical teams.

Thank you for your comment. We removed the comment from line 51.

TABLE 1

Comparison between groups according to pre-operative and intra-operative variables

Variable	Overall (n=892)	Radical Prostatectomy (n=766)	TURP (n=126)	p
Age Mean-median (Range)	68 – 68 (39-87)	68-69 (41-87)	67-67 (39-82)	0.76
RT N (%)	257 (28.9%)	219 (28.6%)	38 (30.1%)	0.40
PIS N (%)	218 (24.4%)	187 (24.4%)	31 (24.6%)	0.52
DM N (%)	111 (12.4%)	88 (11.5%)	23 (18.2%)	0.02
AC N (%)	217 (27.4%)	178 (23.2)	39 (30.9%)	0.03
DOUBLE CUFF N (%)	83 (9.3%)	74 (9.6%)	9 (7.1%)	0.23
CUFF size				0.71
3.5	30 (3.4%)	26 (3.4%)	4 (3.2%)	
4.0	271 (30.4)	239 (31.2%)	32 (25.3%)	
4.5	415 (46.5%)	352 (46.0%)	63 (50.0%)	
5.0	99 (11.1%)	89 (11.6%)	10 (7.9%)	
5.5	35 (4.0%)	28 (3.7%)	8 (6.3%)	
6.0	10 (1.1%)	6 (0.8%)	4 (3.2%)	
6.5	4 (0.4%)	4 (0.5%)	-	

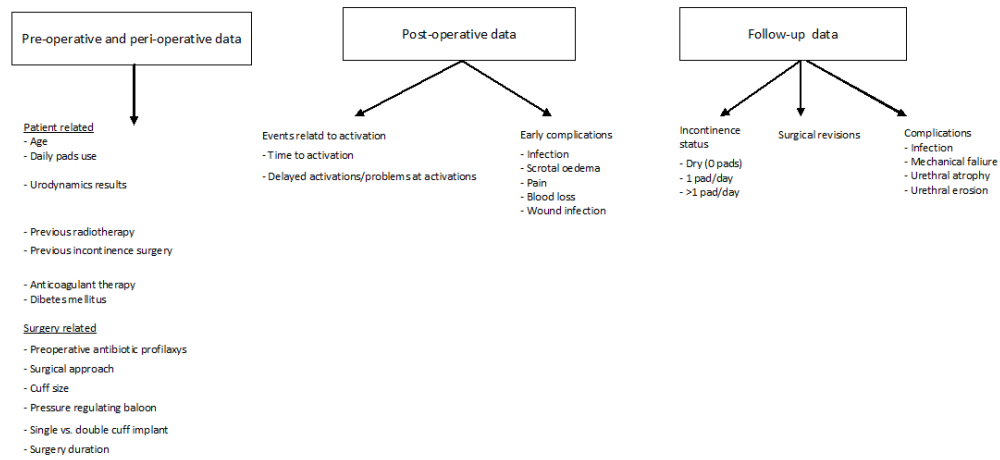
RT: radiotherapy; PIS: previous incontinence surgery, DM: diabetes mellitus, AC: anticoagulation therapy.

TABLE 2
Multivariable logistic regression analysis predicting dry rate and freedom from surgical revision (CI: 95%)

	DRY RATE		FREEDOM FROM REVISION	
Variable	OR	p	OR	p
Age	0.99	0.38	1.02	0.29
RT	1.24	0.21	1.32	0.13
DM	1.22	0.37	1.23	0.38
AC	1.18	0.34	1.39	0.09
PIS	0.51	0.03	0.79	0.30
DOUBLE CUFF	0.61	0.07	0.79	0.68
CUFF size	0.90	0.54	0.87	0.39
ICL	1.18	0.005	1.51	0.00

RT: radiotherapy; PIS: previous incontinence surgery, DM: diabetes mellitus, AC: anticoagulation therapy, ICL: institutional case load.

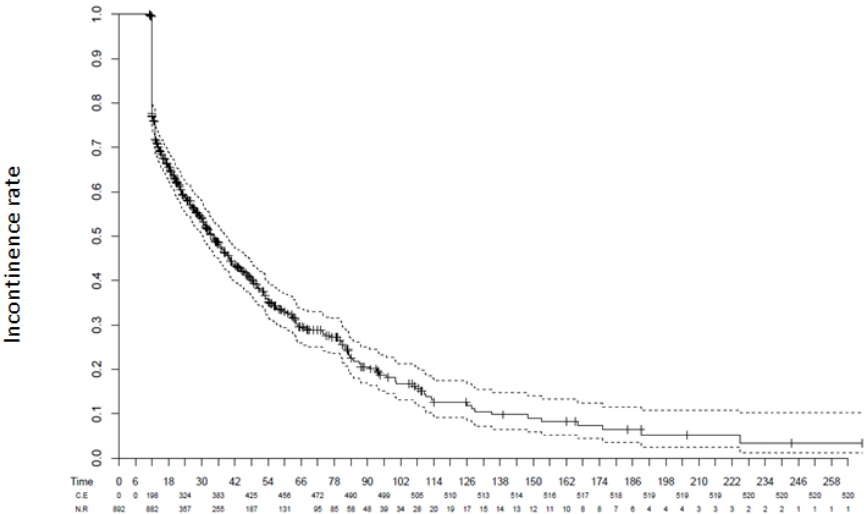
FIG.1 Common template of collected data



Common template of collected data

286x186mm (96 x 96 DPI)

Figure 2
Kaplan-Meier estimate of incontinence rate after surgery over time



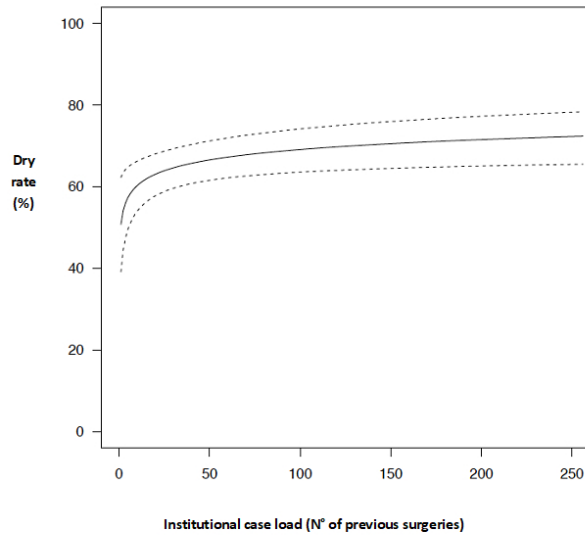
N.R. Number at risk; C.E. Cumulative events

Kaplan-Meier estimate of incontinence rate after surgery over time

216x166mm (96 x 96 DPI)

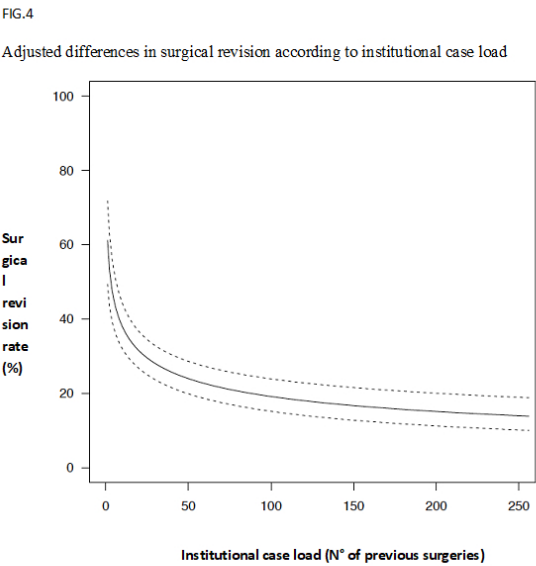
FIG.3

Adjusted differences in dry rate according to institutional case load



Adjusted differences in dry rate according to institutional case load

270x176mm (96 x 96 DPI)



Adjusted differences in surgical revision according to institutional case load

267x178mm (96 x 96 DPI)